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Is the FDA Sexist? Sex and the Drug Approval Process

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Abstract

This paper examines the role of sex in the drug approval process. Medical literature has explored in great depth the many ways in which men and women differ, sometimes dramatically, often in ways that are seemingly unrelated to the physical, anatomical distinctions between the two sexes. After years of intentionally excluding women from critical phases of clinical drug trials, the FDA formally reversed such policies in the 1990s. A number of prescription drugs recently removed from the market disproportionately harmed women as compared to men. Loopholes in the current system have perpetuated the drug approval process's inadequate consideration for the needs of women, thereby subjecting them to a higher level of risk. Efforts to correct for the lack of drug trials aimed to ensure the safety and efficacy for pediatric patients are also reviewed to provide a contrast. While the intentional biases in the system have been addressed, the current drug approval process fails to provide women with the same degree of protection as it does men. A number of issues remain requiring additional study and consideration before a complete solution can be proposed.

“Knowing is not enough; we must apply.
Willing is not enough; we must do.”
– Goethe¹

Introduction

Men and women are different. Sex matters. These two statements are inately obvious. The harder issues arise in discerning how, precisely, men and women are different and when, exactly, sex matters.² This is true in a variety of circumstances, but perhaps not more relevant than with respect to health and medical care.

Medical and scientific advances operate necessarily on the level of generality. Research has indicated how smoking affects the body, but such knowledge cannot precisely predict how a particular smoker will fare. Likewise, without individualized and in-depth study, it is impossible to predict the impact of a dietary regime on any specific individual, but science can safely say that living on fast food will not optimize one’s health. Many daily decisions regarding what we put in our bodies, including everything from the common and habitual consumption of breakfast cereals to the much more deliberate and radical decision to subject the body to toxic cancer treatments, are made without absolute guarantees. Such guarantees would be impractical and largely unnecessary. It is impossible to test, *ex ante*, how every known substance will impact each individual. In addition, such testing would be an enormous waste of resources – discounting the possibility of rare allergic reactions and the role of personal tastes, a bowl of Cheerios will affect my body in pretty much

¹COMMITTEE ON UNDERSTANDING THE BIOLOGY OF SEX AND GENDER DIFFERENCES, INSTITUTE OF MEDICINE, EXPLORING THE BIOLOGICAL CONTRIBUTIONS TO HUMAN HEALTH: DOES SEX MATTER?, title page (Theresa M. Witzmann & Mary-Lou Pardue eds., National Academy Press, 2001).

²*Id.* at ix.

the same way as it will affect yours. The same can be said for the majority of medical and drug treatments, rendering individualized research unnecessary.

Instead of demanding individualized attention, we comfortably rely on statistics generated through research to influence our personal decisions. Based on such general knowledge, I know that it is healthier for me to eat the bowl of Cheerios based on, *inter alia*, calorie and fiber content, than to grab my preferred pop-tarts. I do not need tailored information to show that Cheerios will be beneficial to my body specifically; instead, I am comfortable making this decision based on generally applicable considerations.

While ascribing such thinking to my choice of breakfast foods may seem ridiculous, the same concept may seem more appropriate with regard to medical decisions. I have never been in a medical study, so I have no way of knowing precisely how various chemical compounds affect my physiology. Instead, like the overwhelmingly majority of consumers, I rely on the packaging or the enclosed insert to give me the expected range of reactions and effects. For the overwhelmingly majority of cases and individuals, that information will be more than sufficient, unless, as states above, some unique condition, such as allergy, is present. The information drug manufacturers include in the packaging is derived from the studies and research mandated by the Food and Drug Administration prior to marketing.

In order for my reliance on such information to be reasonable, it must be relevant to me, or at least as relevant as possible for people physically like me. For this to be the case the subjects included in the sample must be randomized, so that as many different “kinds” of people are represented to obtain results generally applicable to as many people as feasible given the restraints (economic costs, time restraints, etc.) of conducting such research. It is logistically impossible to include everyone, so researchers rely on statistical principles to produce robust results that can be extrapolated to the general public.

This method has shown to be a valid research technique over years and years of scientific and statistical research, but only if the research sample chosen adequately represents the general population. If the sample

differs in some relevant manner – for example, if those in the sample metabolize a substance at a different rate than those not in the sample – it would be inappropriate to extrapolate the study’s results to the general public. It follows in some instances, therefore, that if a group were systematically excluded from research samples the results of such studies would be inapplicable with respect to that group. Simple statistical concepts indicate the inappropriateness of using the research findings on anyone of the excluded population.

But that was precisely the treatment women received from the medical and research communities for many years – yet that did not prevent the prescription for use in women of drugs tested only on men. This occurred despite the fact women were not represented in the safety and efficacy studies leading to FDA approval. The past specific exclusion of women from medical research, which will be reviewed here, has been thoroughly documented elsewhere. Instead, the primary focus of this paper is an examination of whether recent attempts to rectify the mistakes of the past have been effective so that women are fully and adequately represented in current medical research with respect to prescription drugs.

Specifically, this paper examines the FDA’s treatment of the role of sex in the drug approval process. Do the current FDA regulations ensure that approved drugs are safe and effective for both sexes? To attempt to answer this question, known differences between men and women, the history of excluding women from medical research, and the FDA’s changing regulations will be reviewed. Additionally, actions to address the lack of research to support the use of prescription drugs in pediatric patients will be summarized. This provides a useful contrast as pediatric patients also have been intentionally excluded from the drug approval process, and concerns about the use of drugs in this subpopulation have risen dramatically in recent years. Unlike with respect to female patients, however, both the FDA and Congress have acted in significant fashions to

ameliorate the situation. In the final section of this paper, the current drug approval process is examined to determine if recent modifications have gone far enough to overcome the mistakes and generally accepted principles of the past.

Many of the issues and concerns expressed in this paper are admittedly equally applicable to other subpopulations, like the elderly, children, or racial minority groups. Perhaps additional reforms in the drug approval process, like those discussed herein with respect to sex differences, are necessary to respond their needs, but such considerations lie beyond the scope of this paper. The decision to limit discussion to sex differences is in no way meant to discount the validity of unique needs of currently underserved subpopulations. While it is possible that drug reactions differ significantly among racial groups, for example, it is also possible that such variances are less extreme than those observed between the sexes. Men and women possess entirely different reproductive systems involving organs not present in the other sex. There is no physical distinction among racial groups that equals the magnitude of this difference between the sexes. Perhaps the strongest analogy can be drawn to the necessity of ensuring the safety and efficacy of prescription drugs for children, as their bodies differ in significant ways from the adult form they eventually will take. The special needs of children have drawn public and congressional attention, leading to a new law designed specifically to address loopholes in the process that left children exposed to unacceptable risk.

In short, perhaps widespread testing at the subpopulation level may be necessary, but further evidence is needed to support such a proposition. It is possible that increased pressure to evaluate sex differences will encourage researchers to note reaction differences among subpopulations like the elderly.

I would also argue that creating and enforcing regulations designed to ensure the safety and efficacy for specific minority groups may prove problematic. The FDA would likely experience even more difficulty in devising racial and ethnic categories than those the Census Bureau went through in creating categories

for its most recent survey. And the lines among groups will continue to blur as the number of interracial individuals, and the cultural and ethnic combinations they represent, increases.

This paper, therefore, focuses specifically on the role of sex in the current drug approval process. Has the FDA done enough to ensure women are fully represented in and protected by the drug approval process?

Terminology: Understanding the Difference Between “Sex” and “Gender”

It is helpful to begin with a clarification of the difference between sex and gender. Although often used interchangeably, the words “sex” and “gender” have distinct meanings. The Institute of Medicine (“IOM”) recommends the following definitions of the terms to clarify and to make consistent the use of the two words. “Sex” refers to an organism’s status as male or female “...according to reproductive organs and functions that derive from the chromosomal complement.” “Gender” should be used to “...to refer to a person’s self-representation as male or female, or how that person is responded to by social institutions on the basis of the individual’s gender presentation.”³ Under this understanding, gender can function as a continuum, whereas sex is a binary condition.⁴

Although it may seem a minute point, it is important to separate these two notions when discussing the role of sex in the drug approval process. Sex differences are biological, representing the genetic or physiological characteristics of being either a man or woman. In contrast, gender reflects the social and cultural distinctions

³*Id.* at 8.

⁴*Id.* at 17.

made based on sex, and how those social constructs impact the individual's image of self.⁵ For the sake of good medicine, it is crucial that researchers are aware of this distinction and do their best to minimize the role gender plays in science while maximizing their sensitivity to sex differences. That is, they must maintain the necessary attention to differences in sex and how they manifest themselves in drug trials while also separating cultural or social distinctions between men and women that have no basis in science.

This paper focuses, therefore, on the role of sex in the drug approval process, not that of gender. Gender most likely also exerts influence on the drug approval process, but in a more subtle fashion. To protect both sexes it is important that the process remain faithful to scientific principles, which in this case means becoming sensitive to the role sex plays in a human's reaction to a drug compound.

The Impact of Sex in Variety of Medical Contexts

Before examining the drug approval process in detail, it will be useful to gain an understanding of the persistent and varied differences that have thus far been found between men and women. "A striking aspect of some sex differences is the consistency with which they appear across populations with vastly different health status profiles and environmental circumstances."⁶ Adding to this is the presence of sex differences in the instances and the symptoms of a variety of diseases, and the often-inexplicable (in light of the current level of scientific and biological knowledge) impact sex has on response to treatment.

⁵Vivian W. Pinn, *Sex and Gender Factors in Medical Studies: Implications for Health and Clinical Practice*, 289(4) J. AMERICAN MEDICAL ASS'N. 397 (2003).

⁶COMMITTEE ON UNDERSTANDING THE BIOLOGY OF SEX AND GENDER DIFFERENCES, INSTITUTE OF MEDICINE, *supra* note 1, at 20.

Through public awareness campaigns, most Americans have become aware of the symptoms of a heart attack. Chest pain, shortness of breath, and pain radiating down the left arm motivate many to seek immediate medical attention. What is less widely known, however, is that these commonly recognized symptoms of a heart attack are less common in women than in men. It is estimated that about 20% of female heart attack victims present symptoms that are not recognized, even by trained medical personnel, as indicators of myocardial infarctions. Instead of the “typical” symptoms, these women experience pain in the upper abdomen or back, nausea, shortness of breath, and sweating. Doctors sometimes misdiagnose these “atypical” complaints as indications of an anxiety attack or indigestion. Instead of receiving immediate medical treatment for their heart attacks, some misdiagnosed women are sent home with prescriptions for Valium to combat their “anxiety” or with antacids to treat their “indigestion.” One twenty-seven year-old woman so treated dropped dead in the parking lot after being dismissed from the hospital emergency room.⁷ Not only do indications of a heart attack sometimes differ by sex, but also the role cholesterol plays as risk factor depends upon an individual’s sex. Both sexes face increased risks for coronary artery disease from having high cholesterol, or more specifically from having a high LDL (low-density lipoprotein) number. This is commonly referred to as “bad” cholesterol. But women must also carefully watch their level of HDL (high-density lipoprotein), also known as “good” cholesterol, as their risk for coronary heart disease increases if this number falls below the normal level. This number may actually be more important for women to monitor than the more commonly acknowledged risk factor of high bad cholesterol. The National Cholesterol Education Panel recommends maintaining HDL levels above 45 for both sexes, but other researchers have suggested that the safe level for women may actually be 70 or higher.⁸

Even among risk factors that affect both men and women, the degree of risk may differ by sex. Holding everything else constant, smoking is more likely to lead to lung cancer in women than in men. And lung

⁷*Popular misconceptions about women’s health and emerging trends in medical research* transcript, TALK OF THE NATION, National Public Radio, Host: Neal Conan (July 30, 2002).

⁸*Id.*

cancer in women is more likely to develop in the periphery of the lungs so that women may experience symptoms of the cancer at a later stage of the disease than similarly afflicted men.⁹ Obviously this delay in disease recognition can have a dramatic effect on the likelihood of survival following diagnosis; as a result, smoking may prove to be more lethal for women than for men.

While the classic symptoms of a heart attack generally match better the experiences of males than females, those of depression more closely comport with the typical female manifestations of the disease than with those exhibited by males. While suffering from depression, men are more likely than similarly depressed women to resort to violence or to abuse alcohol. These atypical symptoms often go unrecognized as indications of the mental health condition, leading many to believe that the incidence of depression is far higher in women than in men. The percentage afflicted in both sexes may, in reality, be closer than previously suspected.¹⁰ Other mental health conditions also afflict the sexes differently. While schizophrenia and bipolar disorders are equally prevalent in men and women, the age at onset of the disease, the pattern of symptoms, and the response to treatment differ by sex. Autism, learning disabilities, and attention-deficit disorder are more common in men.¹¹

Instances of different reactions by sex continue to come to light in startlingly unexpected situations. Such incidences highlight the difficulty of predicting beforehand which diseases or treatments will result in differences, in outcomes or in symptoms, between men and women. For example, researchers in 1992 studied the effects of a new measles vaccine given to children in Haiti. For some inexplicable reason, girls given the vaccine exhibited a significantly higher mortality rate than that seen among the boys. This occurred despite the fact researchers found boys received no preferential health care treatment; the researchers were unable

⁹*Id.*

¹⁰*Id.*

¹¹Pinn, *supra* note 5, at 399.

to cite any biological reason to explain the results.¹²

The list of sex differences is quite long. Urinary incontinence, which afflicts twice as many women as men, typically results from different causes in each sex. For women, it is commonly caused by deficits of urine storage associated with risk factors related to the female pelvic anatomy and physiology; for men, urinary incontinence often results from bladder outlet obstruction.¹³ Irritable Bowel Syndrome (“IBS”) is three times more prevalent in women than men.¹⁴ Women are more likely to recover language ability after a stroke, as well as more likely to develop dangerous ventricular arrhythmias in response to potassium channel-blocking drugs.¹⁵ Kappa opioids, which are morphine-like painkillers, offer powerful, long-lasting relief to women, yet can make pain worse for men at certain doses.¹⁶ Two studies suggest that women are less responsive to anesthesia than men and, as a result, wake up three to four minutes faster after taking same dose of medication per pound of body weight. In general women also suffer more side effects from anesthesia.¹⁷ Some studies have shown that “female” kidneys act more slowly than “male” kidneys. Liver function may also vary by sex.¹⁸ As a result of this difference in liver function, how drugs are metabolized differs between men and women. This, in turn, may explain in part the different reactions seen in men versus women to certain drugs.¹⁹

¹² *Women’s Health Law Symposium, Rutgers School of Law-Newark*, 16 Women’s Rts. L. Rep. 17, 30 (1994).

¹³ Pinn, *supra* note 5, at 398.

¹⁴ *Id.*

¹⁵ COMMITTEE ON UNDERSTANDING THE BIOLOGY OF SEX AND GENDER DIFFERENCES, INSTITUTE OF MEDICINE, *supra* note 1, at 19.

¹⁶ *Pharmacology: Study highlights threat of sex discrimination in the medicine cabinet*, MEDICAL LETTER ON THE CDC & FDA, Aug. 25, 2002, at 15.

¹⁷ *Id.*

¹⁸ *Id.*

¹⁹ Judith Levine Willis, *Equity in Clinical Trials: Drugs and Gender*, FDA Consumer Special Report (1997), available at <http://www.fda.gov/oashi/aids/equal.html>.

The purpose behind this laundry list of differences between men and women is to highlight the significant truth that men and women are different in very significant respects. This concept is generally understood on a shallow, almost comical level (e.g., men are from Venus, women are from Mars), yet has deep, profound implications on an important biological level. When this point is pressed further, men and women obviously have different reproductive organs. And it is also commonly recognized that men, on average, have lower body fat percentages and more muscle than women of same height and weight. Men usually have more abdominal fat and less gluteal-femoral fat than women.²⁰ Yet these commonly recognized physical differences between the sexes hide deeper and far more significant differences that dramatically impact medical care. To be effective and reliable, any research that attempts to explain or predict human reactions or diseases must be sensitive to the distinctions that exist between the sexes.

Sex Differences in General Medical Research and Treatment

Returning to the above discussion of heart disease, many adults have included aspirin consumption in their daily regime specifically to combat heart disease. What many do not know, however, is that the study that led to this general practice included no women subjects. Amazingly, all 22,071 subjects in that study were male physicians. Another significant study on the relationship between cholesterol and heart disease included approximately 15,000 subjects, all of whom were male. Yet another study on the role of caffeine consumption in the development of heart disease counted no women among its 45,589 subjects.²¹ It is entirely possible that the results of those studies are equally applicable to women and well as men, but they demonstrate the

²⁰ COMMITTEE ON UNDERSTANDING THE BIOLOGY OF SEX AND GENDER DIFFERENCES, INSTITUTE OF MEDICINE, *supra* note 1, at 131.

²¹ *Women's Health Law Symposium, Rutgers School of Law-Newark*, *supra* note 12, at 19-20.

focus scientific research placed on male subjects as the norms.

Many such studies were conducted in earlier times (and seemingly prehistoric times with respect to women's rights) when it was widely believed that research conducted with exclusively male subjects could be extrapolated to women with no special consideration for sex differences. It was generally accepted that what worked in men would necessarily work in women without any science to support this assertion. The effect and demise of this common misconception will be discussed below specifically with respect to prescription drug research. But some studies, when considered today, simply defy common sense and cannot be explained with an understanding of the less enlightened perception of sex differences that existed within the research community even a few decades ago.

For example, the National Institutes of Health ("NIH") funded a study on breast and uterine cancer that included male subjects. While men do suffer, albeit at much lower rates, from breast cancer, they obviously do not have uteruses. The justification for the inclusion of male subjects in a study designed to learn about cancer in an organ males do not have was that the focus of the study was on the effect on estrogen metabolism of certain nutrients. As it was believed such metabolism was similarly affected in the two sexes, males were viewed as appropriate subjects of the research.²²

In addition to the lack of attention often paid to women's issues in medical research, in some cases women receive inadequate medical care as a result of the use of men of average weight as the prototypical patients. As a result of the focus on stereotypical heart attack symptoms, which also happen to be more representational of heart attacks in men, heart attacks in women often go undiagnosed and under-treated. Articles in the

²²WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, (GAO-01-754, July, 6, 2001) at 20.

New England Journal of Medicine have shown that female patients get fewer angiograms, fewer cardiac revascularizations, fewer cardiac catheterizations, fewer bypass surgeries, fewer balloon angioplasties, and fewer “clot-buster” drugs.²³ In general, doctors are more hesitant to recommend surgery for their female patients than their male ones. Other studies have shown that men have better access to kidney dialysis and transplantation, despite the fact that women show better response rates to both courses of treatment.²⁴

Growing Acknowledgement of Differing Drug Reactions by Sex

Given the numerous ways in which men and women differ medically and biologically, only some of which were discussed above, it is not surprising that similar patterns have been seen with respect to prescription drugs. As science has become more sensitive to the importance of sex in a variety of medical contexts, many have begun to question and reevaluate its role in the development and approval of prescription drugs.

At the 62nd Congress of the International Pharmaceutical Federation held August 31 through September 5, 2002 in Nice, France, a program entitled Gender Analysis of Medications: Challenges to the Sciences and the Profession of Pharmacy was presented. Various speakers repeatedly acknowledged “...the need to go beyond the ‘70-kg male’ conventional model in clinical studies of medications.”²⁵

One researcher who contributed to the IOM report on sex differences, Carmen Sapienza, Ph.D., of Temple

²³ See, e.g., Ayanian J Z, Epstein A M. Differences in the use of procedures between women and men hospitalized for coronary heart disease. *New England Journal of Medicine*, 1991, 325: 221-225; Steingart R M, Packer M, Hamm P, et al., for the Survival and Ventricular Enlargement Investigators. Sex Differences in the Management of coronary Heart Disease. *New England Journal of Medicine*, 1991. 325: 226-230; Greenberg, Mark A, Mueller, Hiltrud S. Why the Excess Mortality in Women after PTCA? *Vol 87(3)*, March 1993, 1030-1032.

²⁴ *Women's Health Law Symposium*, Rutgers School of Law-Newark, *supra* note 12, at 20.

²⁵ Marianne Rollings, *How genders differ in their response to drugs; Rx Care*, DRUG TOPICS, Oct. 7, 2002, at 129.

University, attended the Nice conference and reported simply that “[e]very cell has a sex. In her opinion, it is necessary to study further the differences between the sexes “from womb to tomb” to ensure that adequate medical care is being provided for all. She also emphasized that there is a distinction between hormonal effects and underlying differences between men and women. And this is a distinction that requires much further research. In her words, “Until the question of sex is routinely asked, and the results – positive or negative – routinely reported, many opportunities to better understand the pathogenesis of disease and to advance human health will surely be missed.”²⁶

The FDA’s Role in the Development of New Drugs

The lack of attention to sex-related differences throughout medical research was perhaps most pervasive with respect to drug development. For years, women were explicitly excluded from drug trials as subjects because researchers and the FDA wanted to prevent the exploitation of women and mistakenly assumed that their inclusion would represent an unnecessary risk and, potentially, an excessive expense.

The FDA plays a crucial role in the development of any drug within this country (and has a tremendous impact on the development of drugs around the world). Before a drug sponsor can test on human subjects, it must submit an investigational new drug application (IND) to the FDA. The IND includes a summary of prior research, which typically includes cellular and animal research, and a general outline of how human studies will be performed. Also included are assurances from the drug sponsors to the FDA that they will do what is necessary to protect the human subjects who may participate in future envisioned trials. “Specifically, the IND application demonstrates that the drug is reasonably safe for subsequent testing in

²⁶*Id.*

humans based on laboratory and animal testing and exhibits enough potential effectiveness to justify its commercial development.” Testing can begin thirty-one days after submission unless the FDA finds that the proposed study is somehow unsafe or it finds some significant flaw with the submitted IND application.²⁷

Following the submission of an unchallenged IND, clinical drug testing of the particular compound proceeds in three stages. Phase I consists of small-scale safety trials, usually using healthy volunteers to ascertain safe dosing levels and to determine toxicity. At this stage the substance’s “pharmacokinetics,” “the time course of the drug’s absorption, distribution, metabolism (biotransformation), and excretion”²⁸, are also evaluated in addition to the dose response. Small-scale efficacy trials commence in Phase II, typically employing the use of a control group to determine the drug’s effectiveness and to monitor for any side effects or adverse reactions. It is in Phase III that full-scale safety and efficacy trials are conducted. A large number of subjects is pooled together to further the research aims begun in Phase II. During clinical trials, sponsors must submit annual IND reports to the FDA, and this overall process of clinical testing usually spans from, on average, two to ten years.²⁹ Assuming the results of Phase III are favorable, a drug sponsor then submits a New Drug Application (“NDA”) as the last major step prior to obtaining approval to market its substance.

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Through this mechanism [IND application and process], which is designed to protect human subjects, and its GLP (good laboratory practices) regulations, the FDA exerts considerable control over the conduct of

²⁷WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 22, at 6.

²⁸COMMITTEE ON UNDERSTANDING THE BIOLOGY OF SEX AND GENDER DIFFERENCES, INSTITUTE OF MEDICINE, *supra* note 1, at 118.

²⁹WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 22, at 6.

clinical trials.” Before the 1962 amendments to its statute, the FDA’s involvement began much later in the investigational process when a sponsor would submit an application to market an already tested product.³⁰ Now, the FDA plays a crucial role in designing the clinical drug trials involving human subjects necessary to support its approval for sale in this country. It also exercises significant control over drug labeling, including information related to indications for use and determining the populations for which the substance has been shown safe and effective.³¹ But once a drug is approved, the use of the substance by a doctor is unregulated by the FDA, though the agency does maintain control over the drug’s marketing. The regulations permit physicians to use an approved drug for people and for conditions not specified by the product label, and this practice is referred to as “off-label use.”³²

A History of Excluding Women from Drug Trials

The basis for the current IND procedures is found in the 1962 amendments to the Federal Food, Drug, and Cosmetic Act that established the present drug approval process. Passage of the amendments was motivated by the thalidomide-related birth defects tragedy.³³ While the motivating tragedy obviously involved the consumption of drugs by women, Congress did not press for the equal treatment of women in the drug approval process. In fact, social forces and ethical concerns pushed the FDA and Congress in the opposite direction.

³⁰ROBERT HIGGS (ed.), *HAZARDOUS TO OUR HEALTH? FDA REGULATION OF HEALTH CARE PRODUCTS* 16 (The Independent Institute, 1995).

³¹WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 22, at 5.

³²Marilynn C. Frederiksen, *The Drug Development Process and the Pregnant Woman*, 47 J. MIDWIFERY & WOMEN’S HEALTH 422, 423 (Nov./Dec. 2002).

³³*Women’s Health Law Symposium, Rutgers School of Law-Newark*, *supra* note 12, at 25.

The ethical issues implicated by medical research received heightened attention following the Nuremberg War Crime Trials after World War II. The judicial process revealed atrocities perpetrated by the Nazis, under the guise of scientific inquiry, on Jews and other groups considered “undesirable.” This knowledge elevated public concern, awareness, and sensitivity around the world regarding the use of human subjects in the name of science.³⁴

The Nuremberg Code of Ethics of 1949 outlined basic moral, ethical, and legal requirements of using human subjects in research. This influenced the growth of a protectionist policy with respect to human subjects within the U.S. federal government. The Tuskegee syphilis study provided a domestic example of the exploitation of a marginalized group for the supposed advancement of science. These ethical abuses colored perception of the thalidomide tragedy so that it was viewed as additional evidence of the need to protect women from the sometimes-unscrupulous scientific community.³⁵ Such factors, in conjunction with the male-centric view of society that dominated contemporary thinking, led to the formal exclusion of women subjects from drug trials.

In response to research abuse concerns and the desire to formalize the drug approval process, the “Federal Policy for the Protection of Human Subjects” (45 C.F.R. §§ 46.101 – 46.124) was promulgated in 1974. The policy included language promoting the notion of “equitable” subject selection,³⁶ but this did not mean that researchers were to ensure that all had equal access to study participation. Rather, its goals reflected concerns about the potential for research abuses that arose from the experiences at Nuremberg. The authors of the government policy sought to prevent the exploitation of one group for the benefit of another, e.g., the use of public patients as test subjects for the benefit of private patients.³⁷

³⁴*Id.*

³⁵COMMITTEE ON UNDERSTANDING THE BIOLOGY OF SEX AND GENDER DIFFERENCES, INSTITUTE OF MEDICINE, *supra* note 1, at 24.

³⁶45 C.F.R. § 46.111(a)(3).

³⁷*Women’s Health Law Symposium, Rutgers School of Law-Newark, supra* note 12, at 26.

In addition to this overall desire to protect vulnerable minorities from exploitation by the majority (or the politically/socially weak and the politically/socially powerful, respectfully), the Federal Policy for the Protection of Human Subjects mentions specific populations warranting additional protection from potential ethical abuses. 45 C.F.R. § 46.111 reads in part: “When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.”³⁸ This language may startle the modern reader for its grouping of women, pregnant or not, with obviously and undeniably vulnerable populations like children or mentally disabled people. But it is interesting to note that women at the time were not so offended because their worries focused on the danger of being exploited by research. As a result, they did not mind being excluded from it and, in fact, welcomed the protection.³⁹

A 1977 FDA guideline entitled “General Considerations for the Clinical Evaluation of Drugs”⁴⁰ explicitly limited, to the point of exclusion, the participation of women of childbearing age in drug research. The term “childbearing” was broadly defined (essentially all menstruating women were deemed of childbearing age⁴¹) so that almost all women were effectively eliminated from the pool of possible study subjects. Under this 1977 guideline, women could participate only in phase III of the clinical drug trial process. As discussed in an above section, this eliminated women from the study during the phases (phases I and II) when significant information about the drug’s pharmacokinetics is discerned. Despite the FDA’s approval of the use of female subjects in the final phase of drug testing, many drug sponsors opted to remain with an exclusively male sample throughout the entire study due to the liability concerns. Many sponsors feared a potential

³⁸45 C.F.R. § 46.111(b).

³⁹ *Women’s Health Law Symposium, Rutgers School of Law-Newark, supra* note 12, at 26.

⁴⁰HEW Publication No. (FDA) 77-3040. (HEW was the Department of Health, Education, and Welfare; it was renamed the Department of Health and Human Services in 1980 following the creation of Department of Education.)

⁴¹ *Women’s Health Law Symposium, Rutgers School of Law-Newark, supra* note 12, at 27.

thalidomide-like disaster and the ensuing legal, political, and economic damages that could result.⁴²

Scientists offered two basic reasons to justify the exclusion of women from their research studies. One argument was that menstruation would complicate their research methodology and evaluation of results, thereby increasing the expense of conducting the work. The second argument focused on potential harms to fetuses should women become pregnant during the course of the study.⁴³ All were wary of the potential public relations and political disaster should the participation in a drug trial by any woman be linked to the deformities of a child born to her. The science of the day did not recognize the pharmacological differences between men and women, so the potential harms of including women as study subjects appeared to overwhelmingly outweigh any perceived benefit.

“Critics of these 1977 guideline have suggested the policy is more a reflection of gender stereotypes, female susceptibility and male invulnerability, than of sound scientific considerations.”⁴⁴ Regardless of what truly motivated the effective prohibition of women from drug research as study participants, the articulated justifications do not make sense and are inconsistent. Researchers were saying both that the hormonal fluctuations associated with the menstrual cycle might affect the response seen in female subjects *and* that results generated from an exclusively male sample were an appropriate basis from which to determine safety and efficacy levels in women, as well as appropriate dosage.⁴⁵ The two positions conflict with each other. The second argument focuses exclusively on potential harms to a fetus through maternal exposure, completely discounting the ability of men to pass damage resulting from dangerous substances on to their offspring.⁴⁶

⁴²WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 22, at 26.

⁴³*Women’s Health Law Symposium, Rutgers School of Law-Newark, supra* note 12, at 20.

⁴⁴*Id.* at 27.

⁴⁵COMMITTEE ON UNDERSTANDING THE BIOLOGY OF SEX AND GENDER DIFFERENCES, INSTITUTE OF MEDICINE, *supra* note 1, at 25.

⁴⁶*Women’s Health Law Symposium, Rutgers School of Law-Newark, supra* note 12, at 21.

Consequently, for a number of years the medical community had no sound scientific basis to justify their prescription of almost all drugs to their female patients. Society's general desire to protect women, the increased attention to ethical abuses in research following the Nazi experience, and an emphasis on women as mothers (as opposed to a lack of regard for men as fathers) all combined to encourage the FDA to generate an explicit policy of excluding women from crucial stages of drug research.

Emerging Acknowledgement of the Need for Female Study Subjects in the Drug Approval Process

Because ethical concerns led to the exclusion of women from much of scientific research, "... the medical community lacks useful, comparable data on conditions that occur disproportionately, that manifest differently, or that require different approaches to diagnosis and treatment in males and females."⁴⁷ This ignorance of the female experience, until recently, pervaded the drug approval process.

At the 62nd Congress of the International Pharmaceutical Federation researchers articulated and explained the need for pharmacokinetic studies and pharmacodynamics on female subjects during phase I and phase II of clinical drug studies, which had been extremely limited under the FDA's 1977 guideline with respect to menstruating women. It is in these two phases that sex differences in metabolism or other processes will be most evident because researchers customarily adjust dosages and study the metabolism of the studied substances at this point in the process. As the dosages evaluated in the final stage are established in the course of phase I and phase II research, it is crucial to allow for the accounting of variations between the sexes, such as the effects of menstrual cycles, menopause, or the lower rate of metabolism generally seen in

⁴⁷COMMITTEE ON UNDERSTANDING THE BIOLOGY OF SEX AND GENDER DIFFERENCES, INSTITUTE OF MEDICINE, *supra* note 1, at 22-3.

women.⁴⁸

The IOM's Committee on Understanding the Biology of Sex and Gender Differences published a report entitled "Exploring the Biological Contributions to Human Health: Does Sex Matter?" in 2001. In addition to answering the question posed in the title with an emphatic "yes," the report stressed the need to ensure the equitable treatment of both sexes during medical research. The following quotation summarizes the report's findings:

Being male or female is an important basic human variable that affects health and illness throughout the life span. Differences in health and illness are influenced by individual genetic and physiological constitutions, as well as by an individual's interaction with environmental and experiential factors. The incidence and severity of diseases vary between the sexes and may be related to differences in exposures, routes of entry and the processing of a foreign agent, and cellular responses. Although in many cases these sex differences can be traced to the direct or indirect effects of hormones associated with reproduction, differences cannot be solely attributed to hormones. Therefore, sex should be considered when designing and analyzing studies in all areas and at all levels of biomedical and health-related research.⁴⁹

The need to infuse each stage of the drug approval process with sensitivity for possible variations by sex is heightened by the examples discussed in the earlier sections of this paper. Many of the sex differences have nothing to do with the obvious differences in anatomy between men and women. In the case of the Haitian vaccine study, for example, researchers were unable to determine an explanation for the higher mortality rates among the female recipients. A few years ago it would have seemed almost ridiculous to think of a kidney as being either male or female, but science has shown that sex has significant impacts at a variety of levels, even at the molecular level. As many sex differences appear startling *ex post*, it is crucial to design the drug approval process *ex ante* so that such differences are noted as early in the process as possible so that an approved drug is truly safe and effective for women and men.

⁴⁸Rollings, *supra* note 25.

FDA's Changing Policy Statements and Guidelines Regarding Women as Study Subjects

The FDA has made significant advances in recognizing the importance of including female subjects since the days of essentially excluding their presence in all but the final stage of clinical drug trials. The rest of this paper will evaluate the effectiveness of these policy changes to determine if the current approach the FDA employs is sufficient to fulfill its mission of ensuring that only safe and effective, for both men and women, drugs reach the market.

The FDA formally reversed its 1977 policy with respect to menstruating women in 1993, noting “fetal protection can be achieved by measures short of excluding women from early trials.”⁵⁰ This guidance, “Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs,” was published in the Federal Register on July 22, 1993.⁵¹ A variety of factors culminated in this policy shift. Obviously the changing role of women in society played a role. As the baby-boomers hit middle age, the women of this cohort group began taking more active roles in their health as their bodies aged and they became more demanding medical care consumers. Their experiences increased awareness of the dearth of information about women due to past research practices designed to protect women from exploitation. In addition, the notion of patient autonomy, so that patients now expect to play a role in making medical treatment decisions instead of deferring automatically to their physicians’ authority, expanded in this country.⁵² These factors combined to create a largely grassroots effort to acknowledge sex differences from a medical standpoint and to encourage researchers to include females in the sample groups studied.⁵³

As the Nuremberg War Crime Trials and the thalidomide tragedy shaped public perception medical research in their times, the growing AIDS crisis of the 1980s significantly impacted the public’s opinions of such

⁵⁰WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 22, at 27.

⁵¹58 Fed. Reg. 39,406 (July 22, 1993).

⁵²*Women’s Health Law Symposium, Rutgers School of Law-Newark, supra* note 12, at 28.

⁵³*Popular misconceptions about women’s health and emerging trends in medical research, supra* note 7.

research. No longer viewed as a threat, research was re-characterized as a public good worthy of increased government and private funding and support. Early AIDS activists of the '80s worried more about the dangers, in the form of lives lost, of slow or inadequate research, than about the potential exploitation of vulnerable groups that had shaped government policy decades before.⁵⁴ Activists fought for expanded access in the earliest stages of clinical research. This is big shift from when women welcomed the protection afforded to them by the FDA's policy of excluding women from early drug research.

The FDA studied the rate of female inclusion in samples used in clinical drug trials from 1983 to 1989. It found the proportions of the sexes roughly approximated that seen in the incidence of disease for which the drug was being developed once the age range of the population being studied was accounted for.⁵⁵ While the sex of the sample generally matched the sex of those afflicted with the given condition, this did not mean there was necessarily enough in either group to show, with statistical sufficiency, the substance safe for either gender. The seemingly positive indication of the report of a growing inclusion of women is further limited by the fact the FDA could not determine the gender of more than one half of participants in submitted annual IND reports.⁵⁶

Another report, this one authored by the General Accounting Office ("GAO"), examined drug sponsors' deliberate attention to the inclusion of women and the sponsors' interaction with the FDA with respect to this issue. The October 1992 report contained a summary of surveyed drug manufacturers that obtained FDA approval between January 1988 and June 1991. Overall, the survey response rate was 92%.⁵⁷ One quarter of the respondents indicated that they did not deliberately recruit women to serve as subjects in study in numbers designed to match their proportion of the subject disease or condition's population. One

⁵⁴ *Women's Health Law Symposium, Rutgers School of Law-Newark*, *supra* note 12, at 28.

⁵⁵ INVESTIGATIONAL NEW DRUG APPLICATIONS AND NEW DRUG APPLICATIONS, 21 CFR §§ 312, 314 (1998).

⁵⁶ WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 22, at 9-10.

⁵⁷ WOMEN'S HEALTH: FDA NEEDS TO ENSURE MORE STUDY OF GENDER DIFFERENCES IN PRESCRIPTION DRUG TESTING, (GAO/HRD-93-17, October 1992) at 19.

half reported that the FDA had asked that women be included in their trials, while the other half said had not been asked.⁵⁸

This 1992 GAO report raised serious concerns about the ability of the drug approval process to determine safety and efficacy for women. Unlike the FDA's own study discussed above, the GAO reported that women were generally underrepresented, meaning fewer women participated in studies, as a proportion, than were found in intended population of users.⁵⁹ Most of the reviewed studies had at least 250 female participants, which was the FDA suggested minimum number, but a full one third included fewer than 250 women.⁶⁰ Many of the responding drug manufacturers admitted that they did not study if the drug in question interacted with female hormones, including those commonly found in oral contraceptives.⁶¹ The report noted that approximately one quarter of childbearing age women use oral contraceptives, and that it is known certain epilepsy drugs can diminish their effectiveness and some antidepressants can increase their effect on the body to the point of toxicity.⁶²

After reviewing the status of sex awareness in the drug approval process, the GAO made several suggestions. It asserted that manufacturers should consider the interplay between their drugs and oral contraceptives, despite the fact the FDA's regulations did not require this investigation.⁶³ As to the FDA, the GAO recommended the Commissioner issue guidance to instruct drug sponsors as to the necessary level of inclusion for both sexes to determine statistical safety and efficacy for men and women. According to this 1992 GAO report, the FDA should also require that drug manufacturers analyze the results of drug studies by sex.⁶⁴ The July 1993 guidance, revising the section of the 1977 guideline that excluded women of childbearing age from participation in early drug studies, specifically mentions the inadequate study of the relationship

⁵⁸*Id.* at 2.

⁵⁹*Id.*

⁶⁰*Id.* at 3.

⁶¹*Id.*

⁶²*Id.* at 6.

⁶³WOMEN'S HEALTH: FDA NEEDS TO ENSURE MORE STUDY OF GENDER DIFFERENCES IN PRESCRIPTION DRUG TESTING, *supra* note 57, at 12.

⁶⁴*Id.* at 13. [Source 14, 13]

between menstrual cycle, menopause, and oral contraceptives and drugs. In this document the FDA also recognizes the earlier exclusionary policy seemed “rigid and paternalistic” when viewed from the more inclusive perspective of the 1990s.⁶⁵ “The early exclusion also may have perpetuated, in a subtle way, a view of the male as the primary focus of medicine and drug development,”⁶⁶ according to the FDA, though the subtlety of this policy is debatable.

In contrast to early justifications for male-only samples focusing on potential risks to fetuses, the 1993 guidance acknowledges women’s right to determine what risk, if any, is appropriate for their bodies and their fetuses. The FDA cited a Supreme Court decision⁶⁷ forbidding the exclusion of pregnant women from certain jobs due to risk and noted the parallel to the their own exclusionary policies.⁶⁸ This guidance directly confronted and rebutted the two articulated reasons for excluding women from medical research. To maximize its scientific value, research needs to evaluate the effect of fluctuating hormones due to menstruating, menopause, and use of birth control pills, regardless of the increased study costs. And it was no longer seen as the government’s or the research community’s responsibility to protect fetuses from potential exposure. Instead, this task fell to the potential mother in question.

Yet there was a significant limit to how far the FDA was willing to go to ensure women had equal access to clinical drug trials. The FDA demonstrated an important shift in thinking with respect to the previously articulated reasons for dramatically limiting female participation in research, but it did not wish to address the biases now inherent to the process as a result of its previous policy. The FDA concluded that there was no “. . . regulatory basis for requiring routinely that women in general or women of childbearing potential be included in particular trials, such as phase I studies.”⁶⁹ This statement was made despite its own growing

⁶⁵GUIDELINE FOR THE STUDY AND EVALUATION OF GENDER DIFFERENCES IN THE CLINICAL EVALUATION OF DRUGS, 58 Fed. Reg. 39,406 (proposed July 22, 1993).

⁶⁶*Id.* at 39,408.

⁶⁷*International Union, United Automobile, Aerospace, and Agricultural Implement Workers, UAW v. Johnson Controls, Inc.*, 111 S. Ct. 1196 (1991).

⁶⁸GUIDELINE FOR THE STUDY AND EVALUATION OF GENDER DIFFERENCES IN THE CLINICAL EVALUATION OF DRUGS, *supra* note 63, at 39408.

⁶⁹*Id.*

appreciation for the sometimes-significant differences between men and women when using the same drug. The guidance issued in 1993 merely recommended the inclusion of men and women “in number adequate to allow the detection of clinically significant gender differences in drug response.” Just as the GAO did in its 1992 report, the FDA suggested drug manufacturers include data analysis of safety and efficacy by sex in NDAs.⁷⁰ But there remains no regulation requiring the inclusion of women at a rate sufficient to yield statistically significant results to support a finding that the substance in question is safe and effective for women patients. In practice, the male study subject has remained the default.

Congress passed the FDA Modernization Act in 1997. One provision of the act amended 21 U.S.C. 355(b)(1) to include the following: “The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials.”⁷¹ The FDAMA Women and Minorities Working Group Report was charged with ensuring compliance with Congress’s explicit instructions. The Group’s first step consisted of a review of existing regulations to see if they adequately responded to the needs of women and minorities by ensuring their proper representation in the studies conducted in the course of the drug approval process. In the alternative, the Group could have found that it lacked sufficient information to make such a determination.⁷²

The Working Group’s review of the then existing FDA guidance began with the 1988 “Guideline for the Format and Content of Clinical and Statistical Sections of New Drug Applications,” which emphasized need for analysis of demographic information in NDAs. The review concluded with the then-recent 1998 regulation, “Final Rule on Investigation New Drug Applications and New Drug Applications,” requiring breakdown of effectiveness and safety data by subgroups, including gender and racial groups. The Group highlighted the

⁷⁰WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 22, at 10.

⁷¹Michael A. Friedman, *FDAMA – Women and Minorities Guidance Requirements* (1998) available at <http://www.fda.gov/cder/guidance/women.pdf>.

⁷²*Id.* at 1.

fact the FDA possessed the authority to refuse to file an NDA should the manufacturer fail to tabulate the necessary information by sex. It then referred back to the 1993 guidance that emphasized the need for sex considerations in drug research.⁷³

With respect to women, the FDAMA Working Group concluded the following:

In the last five years, FDA has issued critical guidance and regulation aimed at ensuring that women are included appropriately in clinical trials and that data are analyzed to ensure that gender information is available and understood. At present, FDA believes

that exclusionary policies regarding the participation of women with childbearing potential in clinical trials will be addressed by the 1998 clinical hold proposed rule, if it is finalized. Therefore, additional guidance is not indicated, and would not be useful, at this time.⁷⁴

Based on such recommendations, the FDA concluded no additional guidance was required to satisfy the amendments of the Modernization Act in this regard. In the Group's opinion, the regulations in place sufficiently protected the needs of subpopulations, so that the drug approval process protected the drug's intended population.

The 1998 rule the Working Group cited in arguing for the adequacy of current FDA handling of sex differences mandates the content and format of NDAs. It requires the drug sponsor to break down the safety and effectiveness data into various demographic subgroups "...including age group, gender, and race, and when appropriate, other subgroups of the population of patients treated, such as patients with renal failure, or patients with different severity levels of the disease."⁷⁵ This followed the FDA's first formal encouragement of such analysis by subgroups in 1995 to support dosage modifications for certain populations, like pediatrics, geriatrics, or patients with renal failure.⁷⁶

The FDAMA Working Group did suggest the creation of a tracking system to monitor submission of racial

⁷³*Id.* at 2.

⁷⁵INVESTIGATIONAL NEW DRUG APPLICATIONS AND NEW DRUG APPLICATIONS, 21 C.F.R. §§ 312 *et seq.*, 314 *et seq.* (1998).

⁷⁶*Id.*

and gender information and the development of "...a program to educate reviewers on the new rule."⁷⁷ The hope was that such a system would act as a further safeguard to ensure the needs of subpopulations, including women, would remain a critical component of the overall drug approval process. As will be seen in the discussion appearing below, these suggestions were not followed, and it can be argued that the FDAMA Working Group was overly optimistic in finding the system sufficient to address the needs of women.

Significant Sex Differences Found in a Study of Recently Withdrawn Prescription Drugs

Despite the FDA's determination that existing guidance and regulations provide sufficient safeguards to ensure approved drugs are appropriate for both sexes, subsequent events raise questions as to the validity of this belief. There is some significant evidence that the drug approval process as it currently functions does not adequately consider the importance of sex, thereby subjecting female patients to an unacceptable and unnecessary level of risk.

In response to a congressional request, the GAO submitted a report dated January 19, 2001 reviewing the drug products withdrawn from the market after obtaining approval from the FDA since January 1, 1997. It is significant to note that the drugs were approved almost four years after the FDA formally reversed its policy regarding the inclusion of women in drug trials. The specific focus of the report was to ascertain if any of the withdrawn product posed a higher degree of risk to women than to men. The GAO collected information from publicly available documents, including FDA documents and review of medical literature, and conferred with drug safety experts. The report's findings were confined to prescription drugs, and the GAO did not review the rate of adverse events related to over-the-counter drugs or vaccines. The GAO

⁷⁷Friedman, *supra* note 71, at 3.

conducted its work from December 2000 to January 2001.⁷⁸

The GAO found that ten prescription drugs were removed from market during the time period studied. Of the ten, four led to more adverse events in women than in men despite being equally prescribed to both sexes. Four other prescription drugs were associated with more adverse reactions in women than in men, but this likely occurred, at least in part, because more women than men consumed them. The report went on: “Of the two remaining withdrawn drugs, one belongs to a class of drugs known to pose a greater health risk for women, but we were unable to find direct evidence that the adverse events that contributed to its withdrawal occurred predominantly in women.”⁷⁹ Only one of the ten withdrawn prescription drugs did not demonstrate a greater degree of harm in any way for women as compared to men.

The four drugs shown to be more dangerous to women than men were: Seldane (antihistamine); Posicor (cardiovascular); Hismanal (antihistamine); and Propulsid (gastro-intestinal). The following four led to a greater number of adverse events in women than men due to the differences in prescription rates by sex: Pondimin (appetite suppressant); Redux (appetite suppressant); Rezulin (diabetic); and Lotronex (gastrointestinal). Propulsid is still available, minimally, on a patient-by-patient basis for those with severely debilitating diseases (e.g., IBS).⁸⁰

It is interesting to note that the time period of this GAO report overlaps with that of the work done by the FDAMA Working Group. When the GAO examined the practical effects of the FDA’s drug approval process, it found some startling results not reflected in the Working Group’s report. That report instead focused on the drug approval process in the abstract. The two approaches led to very different results,

⁷⁸DRUG SAFETY: MOST DRUGS WITHDRAWN IN RECENT YEARS HAD GREATER HEALTH RISKS FOR WOMEN, (GAO-01-286R, January 19, 2001).

⁷⁹*Id.*

⁸⁰*Id.*

and together they show that while the drug approval process may theoretically be unbiased, it may subject women to an unacceptable higher degree of risk than similarly situated men.

It was impossible for the GAO to determine in its review the exact cause of the disproportionate effect of some of the drugs removed from the market. It is entirely possible that real problem was a lack of adjustment in the dosage to account for the lower body weight, on average, of women as compared to men. It is also possible there was a more fundamental, sex-related distinction between men and women that interacted with the prescription drug, so that what was an effective, appropriate substance for use in men was not so for women. But what caused the differing adverse reactions in the two sexes is not the real point. The real point is that the drug approval process, designed to catch potential issues relating to the use of a drug before that drug is widely available on the market, did not work for women. And this was a relatively small study over a restricted period time. It is quite possible the problem is far more pervasive than this study suggests, with more women suffering from a higher rate of side effects or inadequate relief from the use of a drug shown to be safe and effective essentially only for men.

Loopholes in the FDA's Current Approach and the Drug Approval Process

No one would argue that the FDA is intentionally subjecting women to additional risk as compared to men. But the question remains: How could the drug approval process seem responsive to sex differences yet yield significantly different and adverse results for women?⁸¹

⁸¹See, e.g., P. Greenberger, *News from the Society for Women's Health Research: FDA doing poor job of monitoring drugs for sex differences*, 10 J WOMENS HEALTH GEND BASED MED 829 (Nov. 2001).

To answer this question, it is first necessary to understand a bit about administrative law. Regulations have force of law, while a guidance does not bind the FDA or drug manufacturers. A guidance is intended to show how, according to the FDA's current opinion on the status of the relevant laws, statutory and regulatory requirements may be met – but drug sponsors remain free to choose another method to fulfill the prerequisites of market approval. When the guidance on a particular topic is issued before regulation, the FDA applies the earlier guidance in manner consistent with later regulation.⁸²

Crucial differences exist between the 1993 guidance and the 1998 regulation discussed above. As the GAO summarized:

The 1993 guidance specifically discusses the need to analyze clinical data by sex, evaluate potential sex differences in pharmacokinetics, including those caused by body weight, and conduct specific additional studies in women, where clinically indicated. The 1998 regulation requires the presentation of safety and efficacy data already collected in the NDA by sex, but no analysis of such data is required. The regulation does not include a standard for the inclusion of women; it requires only 'presentation of data' without clarifying the extent of data or the format to be used. The regulation does require the identification of any modifications in dose or dose interval because of sex, age, or race, but not weight.⁸³

In other words, the 1998 regulation is much less specific, as it largely discusses how to present the existing and already included information and does not require analysis of data. It does, however, require tabulation of that data by sex in the required annual IND reports.⁸⁴ The 1993 guidance speaks of the importance of analyzing study data to highlight potential differences in drug reactions between the sexes. In order to effectuate this, researchers would have to include enough women so that the results would have any statistical validity. Had the spirit of this guidance had the force of a regulation, so that drug sponsors would have to present pharmacokinetic data specific to women, it would have served as an indirect way of mandating a sufficient proportion of female test subjects, as that would be the only way to produce the requisite data.

Instead, the regulation the FDA promulgated five years after the guidance was far weaker. On its face it

⁸²WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 22, at 10, fn. 15.

⁸⁴*Id.* at 10.

may seem to address the issue of the historical exclusion of women from drug trials, but in reality it does little to mitigate the lingering inequity. The FDA moved subtly from expressing concerns over the lack of women-specific, statistically significant data to a position of merely delineating the proper format for expressing the same male-dominated data.

This is not to say that the language contained in the 1993 guidance, had it had the effect of law, would have done much to ameliorate the situation. But the 1993 guidance does express an acknowledgement of a problem. When the FDA formally confronted that very same problem five years later, it did little to address the true underlying issue – that women are under-represented in study samples – and instead focused on the presentation of data. It is a cosmetic regulation that has little effect on the substance or design of clinical drug trials, and instead focuses on the organization of the data, which remains lacking in a very fundamental regard. That presentation has little value if there are not enough women so that the data analyses by sex have any statistical or scientific relevance.

In 1998 Final Rule, the FDA acknowledges “(1) Different subgroups of the population may respond differently to a specific drug product and (2) although the effort should be made to look for differences in effectiveness and adverse reactions among such subgroups that effort is not being made consistently.” Yet the FDA did not take the further step of requiring constant analysis throughout the process that would help to enable sponsors to detect reactions by subpopulations early in the process. The current drug approval process does not require additional studies or the collection of additional data. As a result, drug sponsors do not have to ensure that subpopulations, such as women, are adequately represented in the main trials conducted for FDA approval or have to conduct additional trials to specifically focus on the safety and effectiveness of the compound in subsets of the population.

It would obviously be much more cost and time efficient to provide for adequate representation (such that

the results by subpopulation would be statistically reliable) within the current drug approval process rather than to require additional studies above and beyond that which the system presently mandates. But the drug approval process does not mandate the inclusion of a given number of subjects from various subgroups, but merely covers how already collected data should be presented. So under the 1998 regulation, the additional “burden” imposed on drug sponsored consisted of tabulating the data by subgroups. Drug sponsors do not have to ensure that the sample includes enough of each group to generate statistically significant results.⁸⁵ The 1998 regulation changed the form of the data, but did not confront the real problem, which can only be addressed by a change in the substance of the data.⁸⁶

One comment submitted to the FDA when this regulation was proposed characterized it as an “empty gesture.” As it fails to mandate a sufficient number of each subgroup population, the regulation would do nothing to correct problem of insufficient information on the effects of drugs on women. The FDA responded to the comment in the final draft of the regulation with the following:

The agency believes that all of these comments reflect a misunderstanding of the intent and scope of the proposed amendments. This rule does not require any change in the number of studies a drug sponsor needs to conduct, nor does it impose any new requirements on the conduct of those studies. The rule refers only to the presentation of data that already has been collected.⁸⁷

In this response, the FDA acknowledges that the regulation will not ameliorate the underlying problem, the one which it itself cited when it noted that subgroups are not being studied in a consistent manner.

Overall, the approach taken in the 1998 regulation is decidedly hands off: “During the past decade, FDA

⁸⁵ INVESTIGATIONAL NEW DRUG APPLICATIONS AND NEW DRUG APPLICATIONS, 21 C.F.R. §§ 312 *et seq.*, 314 *et seq.* (1998).

⁸⁶ See also K. Ramasubbu & D. Litaker, *Gender Bias in Clinical Trials: Do Double Standards Still Apply?*, 10 J. OF WOMEN’S HEALTH & GENDER-BASED MEDICINE 757, 760, 762 (Oct. 2001) (Reviewed articles published in the *New England Journal of Medicine* from 1994 to 1999. Of the 442 randomized, controlled trials discussed therein, 120 met inclusion criteria. On average, 24.6% women were enrolled; gender-specific data was performed in 14% of trials. Authors concluded that the NIH Revitalization Act of 1993 “. . . does not appear to have improved gender-balanced enrollment or promoted the use of gender-specific analyses in clinical trials published in an influential medical journal. Overcoming this trend will require rigorous efforts on the part of funding entities, trial investigators, and journals disseminating study results.” In fact, five trials explicitly excluded women of child-bearing potential without providing a rationale for the decision. According to the authors, “[t]his study adds to already ample evidence that amended clinical trial guidelines have had little effect on improving the scientific basis of medical practice for women.”)

has encouraged demographic subgroup analyses in various guidance documents and other regulatory actions. FDA also has examined the extent of participation of past subgroups in drug development programs.”⁸⁸ But this appears to be as far as the FDA is willing to go.

With any proposal to alter the drug approval process, the FDA must walk a fine line between ensuring safety and allowing much needed medications reach those in need. The requirements of the already-lengthy approval process should not be intensified without substantial justification. The FDA has repeatedly demonstrated an understandable reluctance to adopt regulations formally requiring the inclusion of female subjects due to concerns that such a move would delay the overall approval process and result in higher costs to sponsors, which in turn would harm patients.

What is missing from this understandable position, however, is some substantiation for these fears. Would it be more costly to include more female study subjects? Why? It would obviously be prohibitively expensive to require drug manufacturers to conduct trials specifically designed to screen for potential adverse reactions in women and to evaluate the safety and effectiveness in women alone. But this is not an automatic necessity. Instead, it is possible that women could take the place of some of the men currently participating in the studies. As long as both sexes are sufficiently represented so that the results are statistically robust, the drug trial outcomes will be more applicable to all adults than they are currently.

An article published in the *Journal of Women’s Health and Gender-Based Medicine* reviewed the participation of women in studies discussed in the *New England Journal of Medicine* from 1993 to 1999. Among the 120 controlled trials that composed the sample, only 24.6% of the subjects were women. The authors found the result especially troubling in light of the general understanding and common acceptance of the role of sex differences during the time studied. The authors also questioned the willingness of a prestigious medical

⁸⁸INVESTIGATIONAL NEW DRUG APPLICATIONS AND NEW DRUG APPLICATIONS, 21 C.F.R. §§ 312 *et seq.*, 314 *et seq.* (1998).

journal to publish articles relying on such seemingly limited data, contending that reversing the practice of male-dominated research will require the cooperation of all entities involved in the field of medical research.⁸⁹ This is just one of many articles that have found an endemic under-representation of women in scientific research, as discussed in an earlier section of this paper. How this came about is a product of history, a misguided yet somewhat admirable attempt to protect women and their potential unborn children, from the risks of scientific research. But the unanswered question is why it remains true today, when it is widely understood that the sex of an individual can play a pivotal role in the body's response to a drug. In other words, was it necessary for the other 75.6% of the subjects of the above study to be male? Would the study results be somehow adversely affected had the percentages of men and women been closer to 50%? Could drug sponsors use fewer male subjects to accommodate a larger number of female subjects?

No one would suggest the solution to this problem lies in the inclusion of female subjects to the detriment of male health. But from my research, nobody has examined whether this is really the difficult issue researchers face. If it were possible to equalize the participation rates by sex without increasing the size of the sample, many of the cost issues would be eliminated from any discussion on mandating the inclusion of women at a rate sufficient to generate statistically relevant results. One can safely argue that the majority of compounds consumed everyday has the same effect regardless of whether the consumer is male or female. The crucial issue becomes ensuring, in the relatively few situations where sex matters, enough women are included in the sample so that adverse reactions, variations in response, and necessary dosing modifications are noted as early in the process as possible.

It is, of course, possible that 75.6% of those subjects had to be male in order for the results to have any validity for future male patients. If so, it is then necessary to examine the implications of that fact. Whatever

⁸⁹K. Ramasubbu and D. Litaker, *Gender Bias in Clinical Trials: Do Double Standards Still Apply?*, Vol. 10, No. 8 J OF WOMEN'S HEALTH & GENDER-BASED MEDICINE 757 (October 2001).

validity is thereby protected by including men at a much higher rate than women necessarily applies, with any confidence, to men alone. To offer women the same degree of protection would require a significant increase in the size of the sample, which would obviously increase the cost of research and potentially slow the process. Perhaps this is simply an unavoidable component of drug research. Maybe this is a necessary requirement so the FDA is able to accomplish its mission of ensuring that only safe and effective prescription drugs reach the marketplace.

In its report on the higher rate of adverse events among women for certain drugs, the GAO found three main areas of concern. First, it found a small proportion of women in early clinical studies despite the acknowledged importance of inclusion at this phase. Second, the FDA and drug sponsors are not taking full advantage of existing data to determine potential drug reaction differences between the sexes before the drug enters the market. Third, the FDA currently employs inadequate management tools to assure compliance with regulations; as a result, it does not monitor how many women in trials, ensure that reports include the required tabulations by sex, and train medical officers adequately to review sex issues in every application.⁹⁰

It is apparent from this GAO report that institutional changes are also needed within the FDA. Even if women routinely made up 50% of the samples the problem would persist if it is not adamant about analyzing the implications of the gathered research. It is distressing to find the FDA and sponsors are not taking full advantage of the research presently collected under the current drug approval process. This is a relatively simple oversight for the FDA to correct. Likewise, there is no excuse for the failure of monitoring sufficient to secure compliance with its own regulations. The FDA plays an involved role in the drug approval process

⁹⁰WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 22, at 19.

under the current scheme, so the additional costs, if any, would likely be quite minimal.

Again, while the FDAMA Working Group found that existing procedures were adequate in theory, the GAO found wide variations in practice. On a positive note, the GAO's evaluation found that all of samples included enough women overall to determine statistically the drug's safety for women. In fact, across all phases women were 52% of study participants. But there is still not balanced representation across the three phases of testing. Only 22% of the participants in phase I safety trials, which, as discussed above, are crucial for calibrating dosage levels, were female.⁹¹ In one extreme case, an NDA included no women in the phase I safety trial.⁹² In another, a drug was approved for use in men even though the NDA showed that no men participated in the "pivotal studies."⁹³

In addition to questionable inclusion ratios in certain reports submitted to the FDA, the GAO also found significant problems in the enforcement of the 1998 regulation on the tabulation of research results by sex.

The GAO explained:

We found that new drug application summary documents and investigational new drug annual reports often failed to meet the data presentation requirements of the 1998 regulation. About one-third of the time new drug application summary documents submitted to FDA by drug sponsors did not fulfill the requirements of the 1998 regulations for the presentation of available safety and efficacy outcome data by sex. We also found that 39 percent of the investigational new drug annual reports in our sample did not include the demographic information required by the 1998 regulation. Although FDA has the authority under its 2000 regulation to suspend proposed research for life-threatening conditions if men or women are excluded because of their reproductive potential, it has not yet done so.⁹⁴

Seventeen percent of the NDAs reviewed did not separately tabulate safety information by sex. Separate

⁹¹*Id.* at 3-4.

⁹²*Id.* at 14.

⁹³*Id.* at 13.

efficacy data for men and women was omitted in 22% of the applications.⁹⁵ Both are required under the terms of the 1998 regulation.

Thirty-six percent of the NDAs reported pharmacokinetic differences due to weight, whether or not sex differences were also noted. Twenty-five percent reported differences by sex, but further explained that these differences disappeared once weight was held constant. In all cases, weight was the reported cause of any differences in response between men and women, so no sex-specific dosages were recommended. Three NDAs indicated weight-related dose adjustments based on weight for both male and female patients.⁹⁶ Yet the GAO noted that relatively few of the NDAs described studies comparing women on the drug to a placebo group to determine safety and efficacy specifically in women. And though all of the sex differences were declared clinically insignificant, some were statistically significant.⁹⁷ (“Clinically significant differences are those that are judged to be medically relevant, i.e., have a medical effect that should be taken into account, even if they are not statistically different. Conversely, statistically significant differences may not be considered clinically significant.”⁹⁸) In addition, a significant percentage of the NDAs did not report significant sex differences, and of that group, some failed to include any statistical tests supporting this assertion. As the GAO politely explains, “Failure to describe a statistical test or report a significant difference does not necessarily mean that the difference is not statistically significant.”⁹⁹

The GAO found similar deficiencies in the reviewed IND reports. Of the sample reviewed, fifteen percent of the required annual reports were not submitted; of those submitted, twenty-four percent did not tabulate the number of males and females in the studies as prescribed by the 1998 regulation. “Only 37 percent of

⁹⁵*Id.* at 12.

⁹⁶WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 22, at 17.

⁹⁷*Id.* at 13.

⁹⁸*Id.* at 10, fn. 16.

⁹⁹*Id.* at 15, fn. 24.

the annual reports tabulated the enrolled study populations by sex, as required by the 1998 regulations; 24 percent of the annual reports stated that there were no ongoing studies.”¹⁰⁰ The GAO conducted its review based on seventy-five INDs active in November 2000 and required to submit annual report. The remainder of the INDs, which totaled one hundred in all, consisted of fifteen withdrawn applications, nine for which annual reports were not required, and one for which the FDA could not find the annual report despite records showing it had been filed with the agency.¹⁰¹

As this discussion shows, the FDA’s oversight of submitted IND reports and NDAs is lacking, as a significant number failed to meet the statutory requirements without rebuke from the FDA. To address this in part, the GAO recommended in its 2001 report a number of management tools including a “demographic worksheet” and a “standardized template for the medical officers’ review.”¹⁰² This second component was suggested in response to the documented inattention paid by the reviewers to sex differences in the approval process. FDA reviewers, like the drug sponsors in the written reports, did not deem clinically relevant any sex difference, even those shown statistically significant, in any respect (e.g., safety, efficacy, or pharmacokinetics). Differences in response appearing between the sexes were attributed to weight, when the distinction was discussed, not to any cause related specifically to sex.¹⁰³

Approximately one third of the reviewed NDAs reported higher concentrations of the drug in the bloodstream among those who weighed less, a group that typically includes women. Yet the reviewers did not comment

¹⁰⁰*Id.* at 12-13.

¹⁰¹*Id.* at 13, fn. 21.

¹⁰²WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT, *supra* note 22, at 5.

¹⁰³*Id.* at 15-6.

in their summaries about the potential weight differences that may have existed.¹⁰⁴ In fact, FDA's medical officers are not currently required to discuss sex differences in their reviews.¹⁰⁵ The GAO's report found that the reviewers "...did not discuss in their written reviews why reported differences between men and women in their responses to drugs did not require dose adjustments. In some cases, apparent contradictions in the NDAs about the role of sex or weight within the text of a drug application were not addressed."¹⁰⁶

Essentially, both the drug sponsors and the FDA routinely ignore the weak rules currently in place regarding the presentation of data required under the 1998 regulation. Not only do many of the submitted documents fail to comport with the regulation, but also the FDA fails to sufficiently question and evaluate the data that is provided. The GAO's report concluded:

FDA has not effectively overseen the presentation and analysis of data related to sex differences in drug development. There is no management system in place to record and track the inclusion of women in clinical drug trials or to monitor compliance with relevant regulations, so FDA is unaware that many new drug application submissions failed to meet standards. The agency also does not routinely review the required tabulation of demographic data by sex in the annual reports for drugs in development.¹⁰⁷

While the true protection afforded to women under the 1998 regulation is indeed questionable, it is impossible for it to have even a small degree of effect without stepped up enforcement.

The GAO published a report in January 2003 reviewing the overall operation of the Department of Health and Human Services, of which the FDA is one component. This January 2003 report repeated the themes of the 2001 report. The GAO repeated, "When clinical trials included women, neither drug developers nor

¹⁰⁴*Id.* at 4-5.

¹⁰⁵*Id.* at 17.

¹⁰⁶*Id.* at 18.

FDA took full advantage of the data available to learn more about the tested drug's effects on women and to explore potential sex differences in dosing.”¹⁰⁸ Furthermore, the GAO emphasized that “[w]hile FDA has taken some promising initial steps to address these deficiencies, it is important that the agency finalizes the pilot programs it has under way and give sustained attention to these management issues.”¹⁰⁹

Responses to Similar Concerns Relating to Pediatric Patients

The use of prescription drugs in women is not the only area for which the drug approval process and the FDA have received scrutiny. Many argue that subpopulations are not sufficiently protected by the existing framework. As discussed above, once a drug has received market approval from the FDA its use by physicians is largely unregulated. Doctors have free rein to use the substance in any situation they deem appropriate, even if the drug sponsor never intended it to be used in such a way. Because of the legality of these off-label uses, the drug approval process functions as the only threshold guaranteeing safety.

In recent times, questioning the suitability of the use of approved prescription drugs among pediatric patients has intensified, as this is a common off-label use of prescription drugs.¹¹⁰ Research in pediatric populations had been almost non-existent due to the obvious ethical concerns. What parent would subject his or her child to the risks associated in participating in such trials, regardless of the safeguards imposed and the

¹⁰⁸MAJOR MANAGEMENT CHALLENGES AND PROGRAM RISKS: DEPARTMENT OF HEALTH AND HUMAN SERVICES, (GAO-03-101, January 1, 2003) at 50.

¹⁰⁹*Id.*

¹¹⁰*See, e.g., Pediatric Drug Trials: Women and Children Last?*, 29 J. OF PEDIATRIC GASTROENTEROLOGY AND NUTRITION 125, 126 (Aug. 1999) (“The ethical policy of ‘children last,’ at least as far as drug trials are concerned, must be given serious reconsideration if we are ever to provide the highest quality of care to the children of this country.”).

potential scientific benefit? As a result, most prescription drugs were never formally evaluated for use in children, which also means that the dosing levels were never carefully calibrated in the context of a rigid, controlled trial. This is not to say that doctors haphazardly prescribe those drugs to their young patients. Instead of relying upon the results of studies, doctors institute a modified dosing regime in light of, among other factors, the drug's response history in adults and knowledge of the specific differences in anatomy, metabolism, and pharmacokinetics between children and adults.

But this relatively informal (yet often effective) method of determining use and dosages for children has faced increasing criticism. The FDA stepped in and attempted to expand dramatically the testing of prescription drugs in children. In 1998 it promulgated "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients."¹¹¹ Manufacturers could obtain waivers "...if the product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients."¹¹² With respect to drug products already on the market, the regulation's impact on manufacturers was somewhat mitigated, as it placed the burden upon the FDA to show that pediatric studies were necessary.¹¹³

The United States District Court for the District of Columbia held, in a 2002 decision, that the regulation exceeds the FDA's statutory authority.¹¹⁴ In granting the plaintiff's motion for summary judgment, the court found Congress had spoken directly on this issue through the passage of the FDAMA of 1997, thereby precluding the FDA's jurisdiction to issue this regulation.¹¹⁵ Finding the statute and the agency's regulation

¹¹¹63 Fed. Reg. 66,632 (Dec. 2, 1998).

¹¹²63 Fed. Reg. 66,632, 66,634 (Dec. 2, 1998).

¹¹³63 Fed. Reg. 66,632, 66,668 (Dec. 2, 1998).

¹¹⁴*Ass'n of American Physicians, Inc., et al. v. United States Food and Drug Administration, et al.*, 226 F. Supp. 2d 204 (D.D.C. 2002).

¹¹⁵*Id.* at 212.

“incompatible,” the court held the FDA does not, under current law, possess the power to force manufacturers to conduct drug trials to determine safe use in children.¹¹⁶ The court’s holding applies to both new drugs and already-marketed drugs for which the FDA has met the regulatory burden by showing the necessity of pediatric studies.

As discussed in the court’s opinion, the FDA had proposed the regulation in question at the same time Congress was debating the FDAMA. Despite the agency’s arguments that Congress’s silence on this specific issue signified approval, the court found it far more significant that Congress “... failed to expressly endorse the Pediatric Rule, even though the FDA requested it do so.”¹¹⁷

Litigation on this regulation continues. The most recent published action, as of the writing of this paper, was a denial of a motion for expedited consideration of appeal, which was issued on February 5, 2003.¹¹⁸

Without this regulation, there still remains intact Congress’s attempt to remedy the lack of pediatric studies demonstrating safety and effectiveness through part of the 1997 FDA Modernization Act. To overcome the deficiency, the Act creates incentives for manufacturers to conduct pediatric safety trials, with the choice to do so remaining with the drug’s sponsors. In exchange for documented safety for use in pediatric patients, drug manufacturers are granted an additional six months of market exclusivity following the expiration of a patent or market exclusivity, whichever is longer.¹¹⁹ This section of the 1997 Act included a sunset provision, effect January 1, 2002, and required the Commissioner to report to Congress by January 1, 2001 on the experience and effectiveness of the incentive.¹²⁰ The “Best Pharmaceuticals for Children Act” (“BPCA”) was enacted on January 4, 2002, three days after the sunset provision took effect.¹²¹ This new legislation is

¹¹⁶*Id.* at 220.

¹¹⁷*Id.* at 219-20.

¹¹⁸2003 U.S. App. LEXIS 2079 (Feb. 5, 2003).

¹¹⁹21 U.S.C. § 355(a)

¹²⁰Pub. L. No. 105-115 § 111 (j) & (k), 111 Stat. 296 (1997)

¹²¹Pub. L. No. 107-109, 115 Stat. 1408 (2002)

scheduled to expire on October 1, 2007.¹²²

The new legislation does more than continue the practice of granting an additional six months of market exclusivity when the desired research results are shared with the FDA. Now, the FDA has the authority to request pediatric studies of drugs already on the market if it can show potential health benefits. The FDA is now instructed to weigh the importance of adequate representation of ethnic and racial minorities among the pediatric participants when considering protocols.¹²³ (This may prove meaningless, however, if such subpopulations are not sufficiently represented to generate reliable statistical results). The BPCA also created the “Office of Pediatric Therapeutics” to coordinate all activities within the agency that may involve children’s issues.¹²⁴ This office is also to receive, for a year following the grant of the six-month’s of additional market exclusivity, any adverse event of which the FDA becomes aware.¹²⁵

The BPCA provides a contrast to the approach taken to address sex differences in prescription drug responses. While the BPCA does not mandate pediatric testing, it does recognize and address a potentially serious loop-hole existing in the drug approval process and the unregulated use by doctors of prescription drugs. Congress recognized that socially desirable pediatric studies were not being conducted, perhaps because drug sponsors lacked sufficient market incentives. Unlike as with the well-documented under-representation of women in drug trials, the government did more than encourage the inclusion of children in samples and require the tabulation of pediatric data within the NDA. It went a significant step further by creating a specific incentive to encourage the desired research, and the BPCA provides the FDA with a mechanism to request the information when it determines necessary.

¹²²Pub. L. No. 107-109, 115 Stat. 1408 (2002) at § 8.

¹²³Pub. L. No. 107-109, 115 Stat. 1408 (2002) at § 18(a).

¹²⁴Pub. L. No. 107-109, 115 Stat. 1408 (2002) at § 6.

¹²⁵Pub. L. No. 107-109, 115 Stat. 1408 (2002) at § 17(b).

Congress's actions do not, however, amount to complete solution. Under current statutory and case law, the FDA still does not possess the authority to mandate pediatric trials. Out of practical necessity, prescription drugs remain available for use in children without corresponding studies to guide their use. But it is interesting to note that both Congress and the FDA acted to address the dearth of information about the relationship between children and the prescription drugs prescribed to them.

This discussion of the BPCA is not presented as a model of desirable congressional action to correct for insufficient consideration of sex differences. Instead, it demonstrates that the political capital exists, in Congress and in the FDA, to make changes to expand the protective scope of the drug approval process.

Concluding Thoughts and Unanswered Questions

The fundamental problem with the current drug approval process, involving both the FDA and drug sponsors, is that the male sex is still treated as the baseline, as the norm. This view is still evident in current medical literature.¹²⁶ Women are often treated as a special category, usually referred to in the same breath as minorities. In the end, this is no better than the approach of the seventies that associated pregnant women with truly vulnerable groups like the mentally handicapped or incarcerated individuals. Despite the fact women make up over half of the population, and medical literature is replete with fundamental biological differences between the sexes that extend far beyond the reproductive systems, the current drug approval process does not protect women. And while research has continued to emphasize the often-startling differences between men and women, women are still not adequately represented in medical research. This practice may

¹²⁶COMMITTEE ON UNDERSTANDING THE BIOLOGY OF SEX AND GENDER DIFFERENCES, INSTITUTE OF MEDICINE, *supra* note 1, at 24.

be much less intentional and overt than it was when the drug approval was first institutionalized, but the subtle and insidious lack of attention paid to women patients by researchers and the FDA continues.¹²⁷

It would be inappropriate to extend this position into an argument for the passage of the “Best Pharmaceuticals for Women” Act or the equivalent. Instead, the FDA needs to expand its perception of the drug approval process so that sex differences are properly respected within the existing framework.¹²⁸ The true problem is that the current approval process pretends to address the needs of all, especially all adults, when this is generally not the case. While it may be true that, when reviewed in the abstract, the drug approval process itself is not sexist, the results of the system are, at best, questionable. When significant differences between the sexes are routinely ignored in clinical trials, and recently pulled prescription drugs disproportionately affected women and not men, it is time to question the process.

On average, women live longer, visit doctors more often, undergo complex procedures more frequently, have more lab tests, take more medication, and spend more time in hospitals than men.¹²⁹ Despite being more frequent customers, the medical establishment exhibits a subtle yet wide-ranging bias against women. For example, some recent studies have shown that Medicare provides better coverage for those conditions more frequently seen in men as compared to those conditions more prevalent in women. There is also a pervasive lack of medical research about women and conditions in women. For some, this can have immediate and dramatic effects. For example, many insurance policies exclude coverage for procedures deemed experimental or investigational, so women are disproportionately affected by this seemingly sex-neutral policy.¹³⁰

¹²⁷ See, e.g., K. Ramasubbu and D. Litaker, *Gender Bias in Clinical Trials: Do Double Standards Still Apply?*, Vol. 10, No. 8 J. OF WOMEN’S HEALTH & GENDER-BASED MEDICINE 757, 760 (October 2001) (Five trials published in the *New England Journal of Medicine* during a five year period expressly excluded women of child-bearing potential without detailing specific rational. Why did the researchers do this? Why did the editors of the *Journal* not question this?).

¹²⁸ See also Marianne N. Prout & Susan S. Fish, *Participation of Women in Clinical Trials of Drug Therapies: A Context for the Controversies*, 6 MEDSCAPE WOMEN’S HEALTH E-JOURNAL (Oct. 2001) (After reviewing history of women’s participation in drug trials suggests enforcement of existing regulations and procedures to effectuate necessary changes).

¹²⁹ *Women’s Health Law Symposium, Rutgers School of Law-Newark*, *supra* note 12, at 18.

¹³⁰ *Id.* at 22.

Some commentators have called for the mandatory inclusion of women in studies, such as the clinical drug trials that determine the outcome of the drug approval process, concluding this is only reliable way to ensure that women are sufficiently represented.¹³¹ They acknowledge that such a move would inevitably result in higher research costs, but question the validity of using cost concerns as an argument against the proposal. The underlying assumption of a statement like that is that costs incurred as a result of male-dominated research are appropriate, but the additional expense associated with protecting women would somehow be excessive.¹³² It is interesting to note, however, there is some evidence the FDA believes actions to equalize the rate of participation between the men and women will not be prohibitively expensive.¹³³

The prescription drug approval process can never be perfect. Even in the best-case scenario, the FDA, as a matter of necessity, makes approval decisions based on the results of studies conducted on random samples. There is no way to ensure that rare adverse reactions will appear in the collected data, and certain effects will inevitably become visible only after significant time has passed. Against this risk the FDA must weigh the risks to the population known to need access to treatment for a given condition.¹³⁴ “Once a drug is approved for marketing and used by potentially hundreds of thousands of patients, however, the type, rate, and severity of adverse events caused by the drug can be much different than those detected during the drug’s development.”¹³⁵

The FDA cannot guarantee safety or effectiveness, but it can ensure that the drug approval processes functions so as many people are protected as is feasible. A significant, yet relatively easy, step would be

¹³¹*Id.* at 30. *Cf.* Curtis L. Meinert, *The Inclusion of Women in Clinical Trials*, 269 SCIENCE 795 (Aug. 11, 1995) (Argues against imposition of quotas or the equivalent to ensure adequate representation of sub-populations).

¹³²*Id.* at 29.

¹³³Linda Ann Sherman, Robert Temple, & Ruth B. Merkatz, *Women in Clinical Trials: An FDA Perspective*, 269 SCIENCE 793, 795 (Aug. 11, 1995) (“...FDA expects sponsors to study the full range of patients likely to receive a drug, including both genders, and to analyze the data to determine whether responses in various groups are different. This expectation is not new and implementing it is not likely to add significantly to drug development costs.”)

¹³⁴Higgs, *supra* note 30 at 21.

¹³⁵DRUG SAFETY: MOST DRUGS WITHDRAWN IN RECENT YEARS HAD GREATER HEALTH RISKS FOR WOMEN, *supra* note 78.

for the agency to increase enforcement of the regulations already in place about the presentation of data in the reports submitted to the FDA. It would also not require much of the FDA's resources to educate its evaluators about the importance of sex in drug responses so that it becomes a more significant feature of the drug's overall evaluation.

Beyond these relatively easy changes in practice the FDA should adopt lies the far more difficult and contentious issue about proposals to mandate the inclusion in women subjects in numbers sufficient to generate statistically significant results. The immediate response to such an idea is that it would prohibitively expensive due to the increase in the overall sample size it would entail. But is this true? Are men currently over-represented so that a possible solution would be to replace some male subjects with females? Are women equally willing to participate in clinical drug trials?¹³⁶

For women to enjoy the same level of protection, they must participate in equal numbers in the drug approval process. "Being a research subject does involve risks, but the risks created by our current lack of knowledge about women's health are far more significant."¹³⁷

To address the answer posed in the title of the paper, it is highly unlikely that the FDA is truly sexist in its administration of the drug approval process. It is equally true, however, that the current system continues to rely more on male subjects and to result in more problems for female patients as compared to males. What is needed is a careful, unbiased examination of why researchers continue to rely primarily on male study subjects. Additional research is needed to determine whether incorporating more women in the drug trials, either by supplanting males or in addition to the current number of male subjects, would actually

¹³⁶Dr. Vivian Pinn, director of the Office of Research on Women's Health at the National Institutes of Health, says that is not difficult to get women involved in studies. In fact, women want to know of the existence of the studies and want to participate. *Popular misconceptions about women's health and emerging trends in medical research* transcript, TALK OF THE NATION, National Public Radio, Host: Neal Conan (July 30, 2002).

¹³⁷*Women's Health Law Symposium, Rutgers School of Law-Newark, supra* note 12, at 23.

increase research costs in a dramatic fashion. Once this information is gathered, important policy questions will have to be answered within the agency and by Congress.

If there is no other way to ensure women are represented in the drug approval process but to significantly increase the sample size, thereby increasing the costs of drug research, Congress, the FDA, and the medical research community must evaluate the implications of such a finding. Perhaps the additional expense is simply unavoidable to effectuate the FDA's mission of ensuring only safe and effective drugs reach the market.

Despite its limitations, the drug approval process has proven to be a reliable method for ensuring the safety of drugs, at least for men. The process must be further evaluated so that the same can be said confidently for women.